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ScienceDirect
Chinese Chemical Letters 21 (2010) 287–289
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

A practical synthesis of sarpogrelate hydrochloride and *in vitro* platelet aggregation inhibitory activities of its analogues

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Received 3 July 2009

Abstract

A convenient approach for the preparation of sarpogrelate hydrochloride was developed. Two series of sarpogrelate hydrochloride analogues were designed and synthesized in order to improve their platelet aggregation inhibitory activities, biological tests suggested that these compounds have platelet aggregation inhibitory activities to some extent.

Keywords: Sarpogrelate hydrochloride; Platelet aggregation inhibitor; Synthesis

Cardiovascular diseases, with an estimated 18 million deaths yearly, are the main cause of death and morbidity globally [1]. Therefore, there is an urgent need to discover novel antithrombotic agents as alternatives to existing treatment strategies. 5-HT_{2A} receptor is associated with the contraction of vascular smooth muscle, platelet aggregation, thrombus formation and coronary artery spasms. Accordingly, selective 5-HT_{2A} receptor antagonists may have potential in the treatment of cardiovascular diseases.

Sarpogrelate hydrochloride (SARP, Fig. 1), which is a selective 5-HT_{2A} receptor antagonist marketed in Japan since 1993, has been introduced clinically as a therapeutic agent for the treatment of ischemic diseases associated with thrombosis [2].

2-[2-(3-Methoxyphenyl)ethyl]phenol (**6**) is a key intermediate of SARP, and the synthetic methods for **6** have already been reported [3,4]. In order to synthesize **6** without Grignard reaction or Wittig reaction, we developed another synthetic route, which has advantages as follow: simple process, low prime, and easy industrialization, the total yields of **6** based on **1** was about 53%. The compound SARP was synthesized from **6** in good yields according to the literature [5].

In order to seek novel platelet aggregation inhibitor, we focus our research on studying a series of [2-(ω-phenylalkyl)phenoxy]alkylamines [6–8]. Structure-activity relationship studies indicated that 2-[2-(3-methoxyphenyl)ethyl]phenoxy moiety is a necessary group and those compounds containing nitrogen heterocycle, such as R-96544 and R-102444, showed potent biological activities.

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1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.11.030

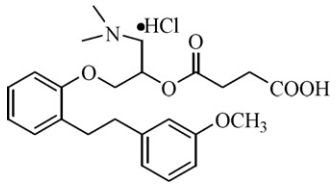
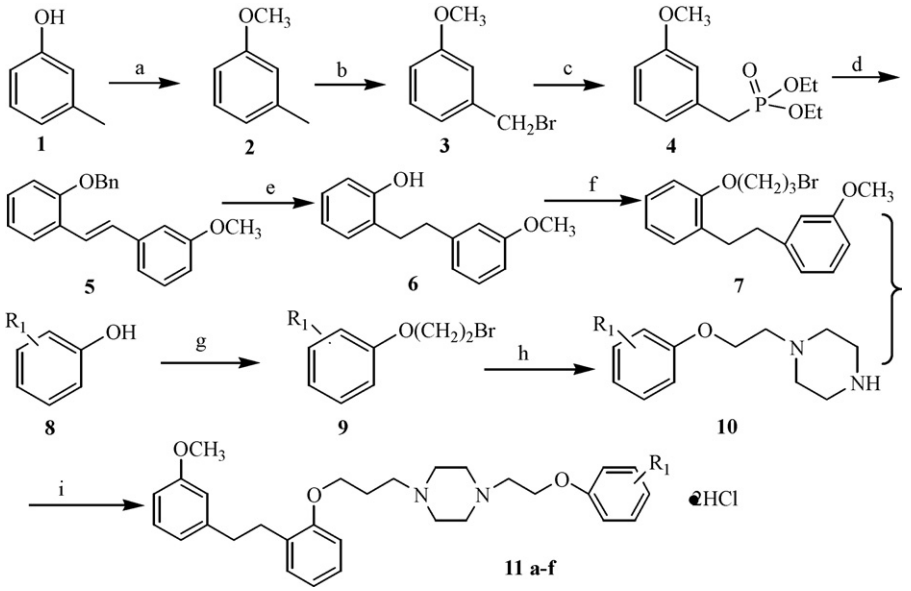


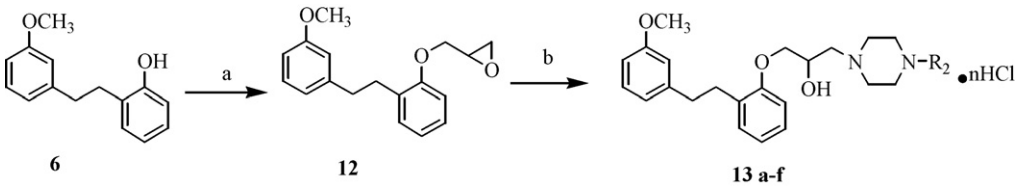
Fig. 1. The chemical structure of SARP.



Scheme 1. Reagents and conditions: (a) $(CH_3)_2SO_4$, NaOH, 50 °C, 5 h, 91.8%; (b) NBS, AIBN, CCl_4, reflux, 5 h, 72.1%; (c) $P(OEt)_3$, 100 °C, 5 h, 92.9%; (d) 2-(benzyloxy)benzaldehyde, NaH, THF, rt, 3 h, 90.5%; (e) 10% Pd/C, H_2(0.1 MPa), rt, 6 h, 94.9%; (f) $Br(CH_2)_3Br$, KOH, t-BuOH, reflux; (g) $Br(CH_2)_2Br$, NaOH, reflux; (h) piperazine, CH_3CN, reflux; (i) K_2CO_3, KI, CH_3CN, reflux, then HCl/EtOH.

A piperazine moiety as a linker is the common characters existed in some cardiovascular drugs, and it is considered as the functional group for keeping the drugs' potent activities. According to the combination principles of medicinal chemistry, substituted piperazines were introduced and two series of analogues were synthesized. The synthetic routes were shown in Schemes 1 and 2.

m-Methylphenol, as the starting material, was treated with dimethyl sulfate, followed by bromination with NBS to give *m*-methoxybenzyl bromide **3**, which reacted with triethyl phosphate to afford diethyl (3-methoxybenzyl)-phosphonate **4**. Coupling **4** and 2-(benzyloxy)benzaldehyde by Wittig–Horner reaction in THF/NaH gave the stilbene **5**, which was first obtained using another route in the early stage of our group's work [9]. Compound **5** was hydrogenated under 0.1 MPa hydrogen at room temperature to produce key intermediate **6**. Compound **6** was treated with $Br(CH_2)_3Br$ to give intermediate **7**. On the other hand, Substituted phenols were converted into bromides **9** using $Br(CH_2)_2Br$, followed by substitution with piperazine in acetonitrile to provide intermediates **10**. **10** was reacted with **7**



Scheme 2. Reagents and conditions: (a) epichlorohydrin, NaH, THF, rt, 6 h and (b) substituted piperazines, triethylamine, isopropanol, reflux, then HCl/EtOH.

Table 1
Platelet aggregation inhibitory activities of target compounds.

No	R_1	IC_{50} (μmol/L)	No	R_2	*n*	IC_{50} (μmol/L)
11a	H	3.6	**13a**	2-Chlorophenyl	1	35.4
11b	3-Methyl	28.2	**13b**	3-Chlorophenyl	1	42.3
11c	2-Chloro	2.1	**13c**	2,3-Dichlorophenyl	1	51.4
11d	3-Chloro	26.4	**13d**	2-Methoxyphenyl	1	13.8
11e	2,3-Dichloro	39.7	**13e**	2-Phenoxyethyl	2	4.3
11f	2-Methoxyl	1.6	**13f**	2-(3-Tolyloxy)ethyl	2	12.3

in acetonitrile, followed by salt formation in HCl/EtOH to provide targets **11a–11f**. In Scheme 2, epoxy derivative **12**, which was obtained from **6** in the presence of NaH in THF by the usual manner, was treated with substituted piperazine in isopropanol, then by salt formation in HCl/EtOH to afford another series of targets **13a–13f**. Date of IR, ^{1}H NMR and MS for representative compounds were given in Ref. [10].

Twelve target compounds were synthesized and evaluated for their platelet aggregation inhibitory activities in vitro according to Ref. [11], with SARP as reference control. Blood was obtained from ulnar vein and was treated with 3.8% sodium citrate (1 part citrate to 9 parts of blood). Platelet-rich plasma (PRP) was prepared by centrifugation at 500 rpm for 5 min. A cuvette containing 250 μL of PRP and 20 μL of test compound solution was placed in the aggregometer and allowed to incubate for 5 min, PRP was challenged with 20 μL of collagen suspension and platelet aggregation was recorded continuously. The inhibitory activities of targets compounds were measured with various concentrations, and the concentration producing 50% inhibition (IC_{50}) was calculated.

The biological results of target compounds were summarized in Table 1. Preliminary biological tests suggested that four compounds displayed remarkable platelet aggregation inhibitory activities. Especially, two compounds (**11c**,**11f**) had lower IC_{50} than that of SARP (2.8 μmol/L). Further modification is currently ongoing in our group to investigate their SAR and explore potential new pharmacological target.

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[10] For compound **5**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, 1H, *J* = 16.4 Hz, –CH═), 7.13 (d, 1H, *J* = 16.4 Hz, –CH═), 6.80–7.60 (m, 13H, Ar–H), 5.15 (s, 2H, $–CH_2–$), 3.83 (s, 3H, $–OCH_3$). ESI-MS (*m*/*z*): 317 $[M+H]^+$. IR (KBr): 3063, 3032, 2977, 2927, 2866, 1601, 1498, 1452, 1243, 752, 697. For compound **6**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72–7.23 (m, 8H, Ar–H), 4.75(s, 1H, –OH), 3.75 (s, 3H, $–OCH_3$), 2.90 (m, 4H, $–CH_2CH_2–$). ESI-MS (*m*/*z*): 227 $[M-H]^-$. IR (KBr): 3526, 3031, 2936, 2860, 1592, 1501, 1455, 1256, 865, 753, 695. For compound **11a**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.08 (brs, 1H, HCl), 13.77 (brs, 1H, HCl), 6.65–7.34 (m, 13H, Ar–H), 4.54 (m, 2H, $–OCH_2CH_2N–$), 4.18 (m, 2H, $–OCH_2CH_2CH_2–$), 3.76 (m, 2H, $–OCH_2CH_2N–$), 3.74 (s, 3H, $–OCH_3$), 3.54–4.01 (m, 8H, piperazine), 3.24 (m, 2H, $–OCH_2CH_2CH_2–$), 2.81–2.93 (m, 4H, $ArCH_2CH_2–$), 2.34 (m, 2H, $–OCH_2CH_2CH_2–$). ESI-MS (*m*/*z*): 475 $[M+H]^+$. IR (KBr): 3409, 2918, 2406, 2292, 1601, 1494, 1454, 1249, 750, 696. For compound **13a**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.96 (brs, 1H, HCl), 6.71–7.39 (m, 12H, Ar–H), 5.44 (m, 1H, $–OCH_2–$), 4.69 (m, 1H, $–OCH_2–$), 4.14 (m, 1H, –CHOH), 3.90 (brs, 1H, –OH), 3.73 (s, 3H, $–OCH_3$), 3.25–3.76 (m, 8H, piperazine), 3.18 (m, 1H, $–NCH_2CHOHCH_2–$), 3.01 (m, 1H, $–NCH_2CHOHCH_2–$), 2.83–2.92 (m, 4H, $ArCH_2CH_2–$). ESI-MS (*m*/*z*): 481$[M+H]^+$. IR (KBr): 3272, 2939, 2836, 2438, 1601, 1494, 1454, 1246, 758, 690. For compound **13e**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.94 (brs, 1H, HCl), 12.79 (brs, 1H, HCl), 6.64–7.34 (m, 13H, Ar–H), 4.60 (m, 1H, $–OCH_2CHOHCH_2–$), 4.50 (m, 2H, $–OCH_2CH_2N–$), 4.13 (m, 1H, $–OCH_2CHOHCH_2–$), 4.06 (m, 1H, –CHOH), 3.73 (s, 3H, $–OCH_3$), 3.49–3.99 (m, 8H, piperazine), 3.87 (m, 2H, $–OCH_2CH_2N–$), 3.25 (m, 2H, $–NCH_2CHOHCH_2–$), 2.81–2.90 (m, 4H, $ArCH_2CH_2–$). ESI-MS (*m*/*z*): 491 $[M+H]^+$. IR (KBr): 3410, 2956, 2381, 1600, 1489, 1454, 1252, 755, 692.
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